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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/785,532	01/17/1997	JOE W. GRAY	2500.124US2	4124

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/785,532	GRAY ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-40 and 48-63* is/are pending in the application.

4a) Of the above claim(s) *29-36,38-40,48-55 and 57-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-28,37,56 and 61-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/14/03*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 26-28, 37, 56, 61-63 are being examined.

This application contains claims drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The following are the remaining rejections.

INTERVIEW

The request for an interview in paper of 12/02/03 is acknowledged. However, due to the presence of many complex, unsolved issues, this Office action is set forth. Applicant is invited to consider this Office action. An interview will be granted upon request, if still deemed necessary.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Rejection under 35 USC 112, first paragraph of claims 26-28, 56, 61-63 pertaining to lack of a clear written description of a probe for use the method for detecting neoplastic cells remains for reasons already of record in paper No.35

Applicant argues as follows:

Suitable probe sequences are readily provided by routine use of probe design software packages or even by visual inspection of the sequence (for example the

complement of SEQ ID NO:9) would readily be recognized as a suitable probe. Consequently, given the level of skill in the art, it is readily apparent that Applicants were in possession of the claimed invention..

Applicant's arguments set forth in paper of 12/02/03 have been considered but are not deemed to be persuasive for the following reasons:

The claims encompass a method for detecting neoplastic cells, using as a probe, a sequence with unknown structure and function, that shares with SEQ ID NO:9 a fragment. Therefore, one would expect that the probe would hybridize to unrelated polynucleotide sequences, that share with SEQ ID NO:9 said common fragment.

The specification fails to describe the probe for use in the claimed method of detecting neoplastic cells, by the test set out in Lilly. The specification describes only a single polynucleotide, SEQ ID NO: 9. Therefore, it necessarily fails to describe a representative number of such species. In addition, the specification also does not describe structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Thus, the specification does not provide an adequate written description of the probe that is required to practice the claimed invention. Since the specification fails to adequately describe the product for use in the method of detecting neoplastic cells, it also fails to adequately describe the method for detecting neoplastic cells.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC 112, first paragraph of claims 26-28, 37, 56, 61-63 pertaining to lack of enablement for a method for detecting neoplastic cells, remains for reasons already of record in paper No.35.

Applicant argues as follows:

1. In the present case, it is established that a large (1.5 Mb) amplification at 20q13.2 is associated with cancers. It is also established that the recited sequence (SEQ ID NO:9) represents a region within this amplification.

Moreover, it is also generally known that chromosomal amplifications such as the one at 20q13.2 occur through gross chromosomal rearrangements such as translocations, inversions, failed segregation, and the like. Such gross rearrangements typically effect all of the nucleic acid sequences within the amplified region. Thus, one of slçill in the art would reasonably expect the recited sequence to be amplified in cells having the amplification at 20q13.2.

In addition, it is noted that SEQ ID NO:9 represents the ZABC-I gene which is also known as ZNF217 (see Exhibit A). ZNF217 (ZabC1) has been shown to be amplified in colorectal cancers having a 20q13.2 amplification (see Hidaka et al. (2000) Clin.Cancer Reï, 6: 2712-2717, attached as Exhibit B).

Contrary to the Examiner's assertion, it is well established that copy number of various genes located within a single continuous amplification (such as is found at 20q13.2) is not independent. Hence the contiguous nature of the amplification.

The recitation of the reference by Hidaka et al is acknowledged.

Applicant's arguments set forth in paper of 12/03/03 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant's arguments, Applicant has not shown that the amplication region detected by the 1.5Mb RMC20C001 probe is contiguous. This is clearly indicated in the specification which discloses that "In highly amplified tumors, the RMC20C001 probe signals were always arranged in clusters by FISH, which indicates location of the amplified DNA sequences in close proximity to one another e.g. in a tandem array" (p.49, lines 16-19). In other words, although the amplication regions are in close proximity to one another, they are not contiguous, and thus one cannot predict whether the polynucleotide sequence of SEQ ID NO:9, which is only 2 Kb in length, is within the amplification regions. Applicant has not shown that the amplified regions detected by the 1.5 Mb probe contain SEQ ID NO:9 used in the claimed method for detecting breast cancer.

Moreover, although SEQ ID NO:9 is amplified in colorectal cancer, as taught by Hidaka et al, this cannot be extrapolated to breast cancer, because different cancers have different etiology and characteristics, and mutation or amplification of a gene in a specific cancer is not necessarily the same as that for the same gene in another type of cancer. For example, Montesano, R et al, 1996, Intl J Cancer, 69(3): 225-235, teach that two different forms of esophagus cancer, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) have different etiological and pathological characteristics, and that a comparison of p53 mutations in these two cancers shows that said mutations differ by their types, frequencies, distribution along the gene and impact on p53 protein

structure (p.231, second column, first paragraph). Similarly, Burmer, GC et al, 1991, Environmental Health perspectives, 93: 27-31, teach that in contrast to sporadic colon carcinomas, mutations in c-Ki-ras are infrequently observed in carcinomas or areas of high-grade dysplasia in patients with chronic ulcerative colitis, and that differences in the frequency, and spectrum of mutations observed in sporadic colon carcinoma and pancreatic carcinoma suggest that a different class of carcinogens may be involved in the initiation of these two tumors (p.27, second column, last paragraph, bridging p.28). Busken, C et al, Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850, teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Thus based on the teaching in the art and in the specification, one cannot predict that SEQ ID NO:9 is amplified in breast cancer.

2. Applicant further argues as follows:

The claims do not read on the use of any probes. To the contrary, the claims, as amended, recite the use of probes that specincallv hybridize to the target sequence under stringent conditions.

The specification at page 6, lines 13-20 states: Bind(s) substantially" or "binds specifically" or "binds selectively" or "hybridizes specifically" refer to complementary hybridization between an oligonucleotide and a target sequence and embraces minor mismatches that can be accommodated by reducing the stringency of

the hybridization media to achieve the desired detection of the target polynucleotide sequence. These terms also refer to the binding, duplexing or hvbridizing of a molecule only to a particular nucleotide sequence under stringent conditions when that sequence is present in a complex mixture (e.g.. total cellular) DNA or RNA.

The probes contemplated for use in the claimed method thus specifically bind (e.g. specifically detect) the recited target sequence and not other non-related sequences that may be present.

Applicant's arguments set forth in paper of 12/03/03 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the definition of "specifically hybridize" in the specification is non-limiting.

The claims 26-28, 56, 61-63 encompass a method for detecting neoplastic cells, using as a probe, a sequence with unknown structure and function, that shares with SEQ ID NO:9 a fragment. Therefore, one would expect that the probe would hybridize to unrelated polynucleotide sequences, that share with SEQ ID NO:9 said common fragment.

In other words, the claimed method is non-specific and would detect unrelated sequences, some of which are taught by the art, such as the sequences taught by Morris et al, 1991, Ionov et al, 1994, Beach et al, 1993, all of record.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Rejection under 35 USC 112, first paragraph of claims 26-28, 37, 56, 61-63 pertaining to lack of enablement for a method for detecting "neoplastic cells" having an increased copy number of nucleic acid sequences at chromosome region 20q13.2, by detecting a copy number of "any nucleic acid" in chromosomal region 20q13.2, remains for reasons already of record in paper No.35.

Applicant argues as follows:

The claim simply is not directed to detecting any neoplastic cell. To the contrary, the claim is directed to a method of detecting a neoplastic cell having an increased copy number of nucleic acid sequences at chromosome region 20q13.2. The Examiner has offered no basis or rationale for ignoring express language on the face of the claim to in her assertion that the claim reads on a method of detecting any neoplastic cell. In making her rejection, the Examiner simply reads the claim more broadly than the plain language permits and this is an improper basis for a "scope rejection".

Moreover, as explained above, Zabc1 (SEQ ID NO:9) is located within the 20q13.2 amplicon and as asserted in the specification and supported by published data çe.g., Exhibit B), Zabc1 is a gene that is amplified in the 20q13.2 amplicon.

Applicant's arguments set forth in paper of 12/03/03 have been considered but are not deemed to be persuasive for the following reasons:

The specification only discloses a single cancer, breast cancer that is associated with an increased number of copies of genes detected by the 1.5Mb probe, the RMC20C001 probe.

Applicant has not shown that any other neoplastic diseases also have an increased number of copies of genes detected by the 1.5Mb probe, the RMC20C001 probe. It is noted that different cancers have different etiology and characteristics, and mutation or amplification of a gene in a specific cancer is not necessarily the same as that for the same gene in another type of cancer, in another cancer tissue, *supra*.

Further, although Zabc1 or SEQ ID NO:9 is a gene that is amplified colon cancer, this does not mean that the amplication of parts of the 20q13.2 chromosome in breast cancer would include SEQ ID NO:9. In other words, the 20q13.2 amplicon for colon cancer in colon tissue is not necessarily the same as the 20q13.2 amplicon for breast cancer in breast tissue, because mutations of genes in different tissues are unexpected phenomena and are independent of each other.

Moreover, by detecting a copy number of "any nucleic acid" in chromosomal region 20q13.2, one would not expect that breast cancer would be detected, because there is no correlation between breast cancer and increased in copy number of any nucleic acid" in chromosomal region 20q13.2. Applicant has not addressed this issue.

2. Rejection under 35 USC 112, first paragraph of claims 26-28, 37, 56, 61-63 pertaining to lack of enablement for a method for detecting in "any sample" the presence or absence of neoplastic cells having an increased copy number of nucleic acid sequences at chromosome region 20q13.2, by detecting a copy number of a nucleic acid in chromosomal region 20q13.2, remains for reasons already of record in paper No.35.

Applicant argues as follows:

The Examiner misreads the claims. The claim is plainly directed to detecting the presence or absence of neoplastic cells and the neoplastic cells are neoplastic cells having increased copy number of nucleic acid sequences at chromosome region 20q13.2. . In other words. in a cancer lacking a 20q13.2 amplification the method will detect the absence of neoplastic cells having an increased copv number of nucleic acids at 20q13.2. The method thus works as claimed in any cell or tissue and is fully enabled for such.

The Examiner's comment regarding the alleged lack of use for the claimed detection of the absence of neoplastic cells in a sample (see Office Action, page 9, lines 13-14) simply does not negative enablement or indicate that the scope of the claims is overbroad.

The Examiner's allegation regarding the limited use of the claimed invention in certain contexts samples goes to utility rather than enablement. There is, however, no doubt that a method of detecting neoplastic cells has a specific, substantial and credible utility.

Applicant's arguments set forth in paper of 12/02/03 have been considered but are not deemed to be persuasive for the following reasons:

Other than breast cancer tissue, it is unpredictable that any other tissues would have amplification of genes detected by the 1.5Mb probe, the RMC20C001 probe, because mutations of genes in different tissues are unexpected phenomena and are independent of each other. The specification only discloses a single cancer, breast cancer, detected in a single tissue, breast cancer tissue, that is associated with an

increased number of copies of genes detected by the 1.5Mb probe, the RMC20C001 probe.

Thus one would not know how to make and use the claimed method when any tissues other than breast tissue are used in the claimed method. This is clearly an enablement issue and not a utility issue.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

SUSAN [illegible], PH.D
PRIMARY EXAMINER

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

March 02, 2004